# Deciphering the interactions between the immune system and cancer cells to enable precision medicine

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## I. Extended Abstract

One of the missions of Precision Medicine (PM) is to tackle the issue of interpreting the mass of malignant cells or tumor nature to design the most appropriate strategy to treat patients [1], [2]. To this extent, recent therapies focus on the tumor microenvironment (TME) and, more specifically, on the role of the immune cells in it [3]. Such treatments take advantage of the intrinsic properties of the immune system: malignant cells are recognized as a pathogen and in turn will be utterly destroyed [4]. Therefore, successful-to-thrive tumor means that cancer cells are evading immunological attacks among other anti-tumoral mechanisms.

The field of PM has made progress thanks to the evolution of the concept of disease. By leaving behind the application of one-layered approach studies, diseases are now understood as an interconnected and multidimensional multilayerered network of molecular mechanisms of biological processes [1], [5]. Particularly, Cancer disease was traditionally explained as the aftereffect of somatic mutations of cancer related genes [6], [7], [8]. Actually, most typical cancer-associated driver genes such TP53 or BRCA2 are usually found mutated in tumors [6], [7], [8] as they happen to be key regulators of cell death processes [9], [10]. However scientific studies solely based on isolated mutations produced on these type of genes are not able to explain nor predict the whole process and development of the disease [11].

In a further complication, every tumor is unique [12]. This is due to the convoluted relationship existing between cellular processes such as genetic and epigenetic modifications that may alter the intracellular and extracellular composition and, by extension, the TME [13]. For instance, results obtained by The Cancer Genome Atlas (TCGA) from the transcriptional analysis of 10,000 tumor samples from different subjects and 33 different types of cancer pointed out the existing variation of immune cells population across tumors (Figure 1) [14].

Against the general tendency to study the effect of cancer-associated somatic mutations on a genetic level, the present work pays attention to their impact from a structural point of view in the TME. Clearly, it is not the same to find a mutation affecting the catalytic site of a protein than in a non-functional area of the structure [15], [16]. The goal is to analyze the Biology underlying variation on the tumor immune infiltration and to what degree this can be explained by the location of missense mutations on the protein structure. More specifically, major emphasis has been put on the mutation occurring on the interaction or interface area of these proteins.

### A. Methods

We hypothesized that all protein residues involved in the same interface create a functional region within a protein. Mutations within the same functional region are more likely to have the same effect than mutations in different functional regions. To identify such interfaces, we analyzed 421582 protein coordinate files from the Protein Data Bank. We defined protein interfaces as all the residues in close proximity to either other proteins, nucleic acids or small ligands. We then generated used a linear model to analyze 1839298 missense somatic mutations from 10224 patients from The Cancer Genome Atlas:

$$\begin{aligned}\text{Leukocyte fraction}_i = \beta_0 &\\ &+ \beta_1 \text{Cancer Type}_i\\ &+ \beta_2 \text{Tumor Mutation Burden}_i\\ &+ \beta_3 \text{Mutation 3D Location}_i\\ &+ \beta_4 \text{Biological Sex}_i\\ &+ \epsilon_5\end{aligned}$$

with i = 1, ... , n; being n the total number of TCGA patients.

### B. Results

We generated a catalogue of 145046 protein interfaces (52237 protein-protein, 5329 protein-nucleic acid and 87480 protein-ligand). Our preliminary results show that 13379 of these interfaces, when somatically mutated, correlate with changes in the quantity of the immune infiltrate in the tumor microenvironment.

For example, mutations on the interface between peptidylarginine deiminase 1 (PAD1) and Ca2+ atoms, which correspond to the catalytic site of the enzyme, were found in patients with higher levels of immune infiltrate than cancer patients with other mutations in the same gene or no mutations in the gene at all. Interestingly, PAD1 is in charge of protein citrullination since it converts arginine to citrulline, being these citrullinated proteins target of antibodies [ref]. Perhaps, in these patients, if the levels of citrulline is low due to the mutation on the catalytic site, less number of citrullinated

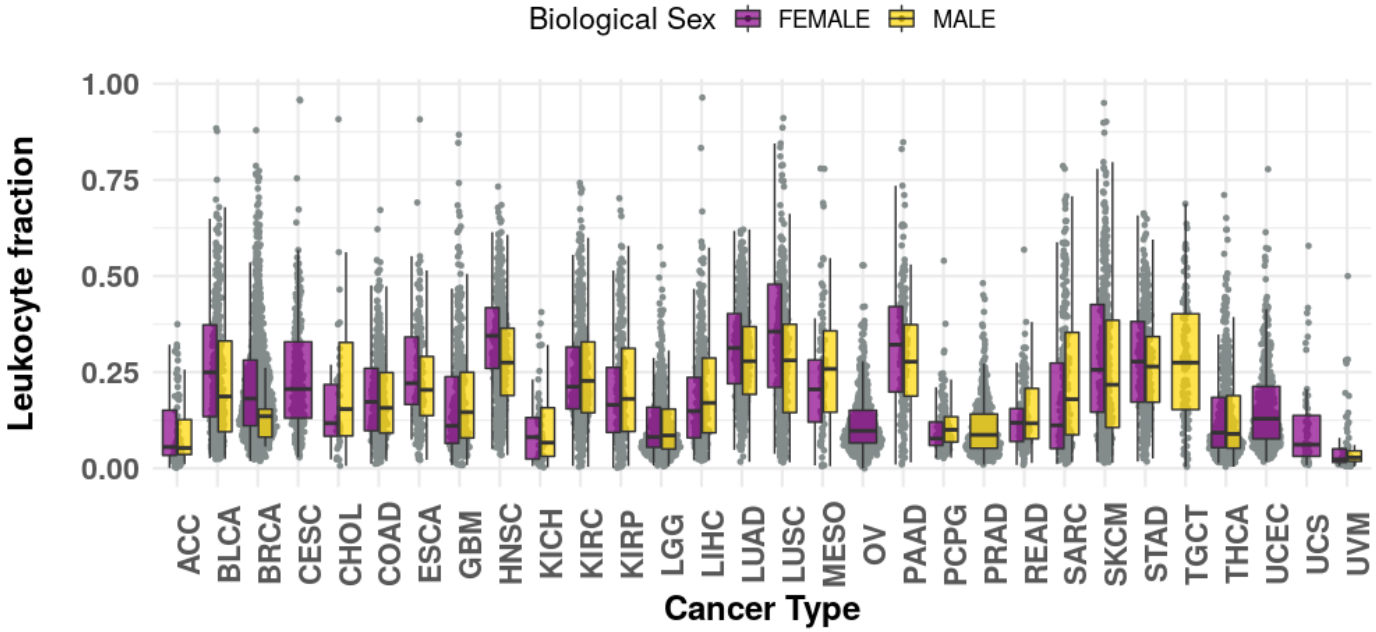


Fig. 1. Distribution of leukocyte fraction (synonym of immune infiltrate) across the different TCGA samples. Each dot corresponds to an individual tumor sample and the samples are grouped according to the Cancer type classification. Box-plots summarize each sex contributions to the leukocyte fraction distribution.

proteins will be found and lead to lower immune attack to the cancer cell.

### C. Future work

Next steps will focus on the global study of all the mutations of the protein interfaces. It would be interesting to be able to discriminate which mutations have higher effects and why, in terms of tumor immune-infiltrate. Moreover, linear models will be cross-validated to rise the statistical power of the results.

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